

REMARKS

The specification is amended above to insert a reference to related cases.

The specification and claims are amended above to insert a reference to Sequence ID No.

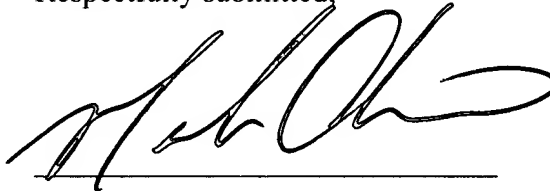
Applicants respectfully submit, a written Sequence Listing and a DOS Text CRF Sequence Listing file "2556usop.ST25.txt" on the enclosed 3.5" IBM PC/AT computer disk.

The undersigned hereby certifies that the CRF and the written Sequence Listing are the same in content.

No amendment of inventorship is necessitated by these amendments.

Early allowance of the claims is requested. Should the Examiner believe that a conference with applicants' attorney would advance prosecution of this application, the Examiner is respectfully invited to call applicants' attorney.

Respectfully submitted,



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MARK-UP of the SPECIFICATION SHOWING CHANGES MADE

Please substitute the following paragraph [06] for paragraph [06] on pages 2-3 of the specification.

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[06] Accordingly, the present invention provides:

- (1) a composition that retards the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer, which contains a hormonal agent,
- (2) the composition according to (1) above, wherein said hormonal agent is an LH-RH derivative,
- (3) the composition according to (2) above, wherein said LH-RH derivative is an LH-RH agonist,
- (4) the composition according to (3) above, wherein said LH-RH derivative is a peptide represented by the formula:
5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO:1)
wherein Y represents a residue selected from among DLeu, DAla, DTrp, DSer(tBu), D2Nal and DHis(ImBzl); Z represents NH-C₂H₅ or Gly-NH₂, or a salt thereof,
- (5) the composition according to (3) above, wherein said LH-RH derivative is 5-oxo-Pro-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NH-C₂H₅ (SEQ ID NO:2) or an acetate thereof,
- (6) the composition according to (1) above, which contains in addition to a hormonal agent an agent that inhibits the action of a cell growth factor or a receptor thereof,
- (7) the composition according to (6) above, wherein said cell growth factor is ① EGF or a substance possessing substantially the same activity as it, ② insulin or a substance possessing substantially the same activity as it or ③ FGF or a substance possessing substantially the same activity as it,
- (8) the composition according to (1) above, which is a preventive/therapeutic composition for prostatic cancer, ovarian cancer, cervical cancer or breast cancer,
- (9) use of a hormonal agent for retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer,

(10) use of a hormonal agent for producing a pharmaceutical for retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer, and

(11) a method of retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer in a mammal carrying a hormone-dependent cancer, comprising administering a hormonal agent to said mammal. --

Please substitute the following paragraph [07] for paragraph [07] on pages 3-6 of the specification.

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[07] Furthermore, the present invention provides:

(12) a method of retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer, comprising using a hormonal agent,

(13) a method of retarding the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer, comprising using a hormonal agent and a agent that inhibits the action of a cell growth factor or a receptor thereof,

(14) a method of treating/preventing a cancer, comprising using a hormonal agent to retard the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer,

(15) a method of treating/preventing a cancer, comprising using a hormonal agent and an agent that inhibits the action of a cell growth factor or a receptor thereof to retard the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer,

(16) a method of suppressing the metastasis/recurrence of a cancer, comprising using a hormonal agent to retard the transformation of a hormone-dependent cancer to a non-hormone-dependent cancer,

(17) a method of suppressing the metastasis/recurrence of a cancer, comprising using a hormonal agent and an agent that inhibits the action of a cell growth factor or a receptor thereof to retard the transformation of a hormone-dependent cancer to a

non-hormone-dependent cancer,

(18) the method according to (11), (12), (13), (14), (15), (16) or (17) above, wherein said hormonal agent is an LH-RH derivative,

(19) the method according to (18) above, wherein said LH-RH derivative is 5-oxo-Pro-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NH-C₂H₅ (SEQ ID NO:2) or an acetate thereof,

(20) the method according to (13), (15) or (17) above, wherein said cell growth factor is ① EGF or a substance possessing substantially the same activity as it, ② insulin or a substance possessing substantially the same activity as it or ③ FGF or a substance possessing substantially the same activity as it,

(21) the composition according to (7) above, wherein said cell growth factor is EGF or a substance possessing substantially the same activity as it,

(22) the composition according to (7) above, wherein said cell growth factor is insulin or a substance possessing substantially the same activity as it,

(23) the composition according to (7) above, wherein said cell growth factor is FGF or a substance possessing substantially the same activity as it,

(24) the composition according to (20) above, wherein said cell growth factor is EGF or a substance possessing substantially the same activity as it,

(25) the composition according to (21) above, wherein said cell growth factor is insulin or a substance possessing substantially the same activity as it,

(26) the composition according to (21) above, wherein said cell growth factor is FGF or a substance possessing substantially the same activity as it,

(27) the composition according to (7) or (21) above, wherein said EGF or substance possessing substantially the same activity as it is EGF or heregulin (HER2 ligand),

(28) the composition according to (7) or (22) above, wherein said

insulin or substance possessing substantially the same activity as it is insulin, IGF-1 or IGF-2,

(29) the composition according to (7) or (23) above, wherein said FGF or substance possessing substantially the same activity as it is aFGF, bFGF, KGF, HGF or FGF-10,

(30) the composition according to (20) or (24) above, wherein said EGF or substance possessing substantially the same activity as it is EGF or heregulin (HER2 ligand),

(31) the composition according to (20) or (25) above, wherein said insulin or substance possessing substantially the same activity as it is insulin, IGF-1 or IGF-2,

(32) the composition according to (20) or (26) above, wherein said FGF or substance possessing substantially the same activity as it is aFGF, bFGF, KGF, HGF or FGF-10,

(33) the composition according to (6) above, wherein said receptor is an EGF receptor, a heregulin receptor (HER2), insulin receptor-1, insulin receptor-2, IGF receptor, FGF receptor-1 or FGF receptor-2,

(34) the composition according to (13), (15) or (17) above, wherein said receptor is an EGF receptor, a heregulin receptor (HER2), insulin receptor-1, insulin receptor-2, an IGF receptor, FGF receptor-1 or FGF receptor-2,

(35) the composition according to (6) above, wherein said receptor possesses tyrosine kinase activity,

(36) the method according to (13), (15) or (17) above, wherein said receptor possesses tyrosine kinase activity, and

(37) the method according to (9), (10), (11), (12), (13), (14), (15), (16) or (17) above, wherein said cancer is prostatic cancer, ovarian cancer, cervical cancer or breast cancer.--

Please substitute the following paragraph [17] for paragraph [17] on page 8 of the specification.

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[17] As an LH-RH derivative, there may be mentioned an LH-RH agonist or an LH-RH antagonist. As an LH-RH antagonist, there may be used, for example, a peptide represented by General Formula [I]:

X-D2Nal-D4ClPhe-D3Pal-Ser-A-B-Leu-C-Pro-DAla-NH₂ (SEQ ID NO:3)

wherein X represents N(4H₂-furoyl)Gly or NAc; A represents a residue selected from among NMeTyr, Tyr, Aph(Atz) and NMeAph(Atz); B represents a residue selected from among DLys(Nic), DCit, DLys(AzaglyNic), DLys(AzaglyFur), DhArg(Et₂), DAph(Atz) and DhCi; C represents Lys(Nisp), Arg or hArg(Et₂), or a salt thereof.--

Please substitute the following paragraph [18] for paragraph [18] on pages 8-9 of the specification.

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[18] As an LH-RH agonist, there may be used, for example, a peptide represented by General Formula [II]:

5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO:1)

wherein Y represents a residue selected from among DLeu, DAla, DTrp, DSer(tBu), D2Nal and DHis(ImBzl); Z represents NH-C₂H₅ or Gly-NH₂, or a salt thereof. A peptide wherein Y is DLeu and Z is NH-C₂H₅ (leuprorelin) or a salt thereof (e.g., acetate) (5-oxo-Pro-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NH-C₂H₅ (SEQ ID NO:2) or acetate thereof) is particularly preferred.--

Please substitute the following paragraph [70] for paragraph [70] on pages 21-22 of the specification.

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[70] 5 ml of a cell suspension (2×10^5 cells/ml) of the human prostatic cancer cell line LNCaP (ATCC (American Type Culture Collection) Catalog No. CRL1740, J.S. Horoszewicz, Cancer Res. 43: 1809-1818 (1983)) was dispensed to 60 mm Petri dishes and cultured at 37°C in the presence of 5% CO₂ overnight. The medium was replaced with a medium containing a preset concentration of cyproterone acetate (Sigma; Cat. No. C-3412) and cultivation was continued at 37°C in the presence of 5% CO₂ for 3 days. After the medium was removed, RNA was extracted from each Petri dish by the acidic guanidine isocyanate/phenol/chloroform method. With these RNA extracts as templates, complementary DNAs were synthesized using an oligo-dT adapter primer (Takara Shuzo) as a primer, to yield PCR reaction templates. Primers specific for the receptor type tyrosine kinase group were synthesized on the basis of sequences common to the kinase regions, i.e., HisArgAspLeuAlaAla (SEQ ID NO:4) and SerAspValTrpSer (SEQ ID NO:5) (Hanks et al., 1988). Specifically, 5'-CA(C/T)(C/A)GGGA(C/T)(C/T)TGGC (A/T/C)GC (sense primer) (SEQ ID NO:6) and 5'-A(A/G)CTCCA(A/C)AC(A/G)TC(A/G)CT (antisense primer) (SEQ ID NO:7) were synthesized for EGF receptor-like kinase, 5'-CA(C/T)(C/A)G(G/A)GAC(C/T)T(G/T)GC(A/T)GC (sense primer) (SEQ ID NO:8) and 5'-A(A/G)CTCCA(A/C)ACGTC(A/C)GA (antisense primer) (SEQ ID NO:9) for insulin receptor-like kinase, and 5'-CA(C/T)(C/A)G(G/A)GAC(C/T)TGGC(A/G)GC (sense primer) (SEQ ID NO:10) and 5'-A(A/G)GACCA(G/C)AC(A/G)TC(A/G)CT (antisense primer) (SEQ ID NO:11) for PDGF receptor-like kinase and FGF receptor-like kinase. An amplification reaction was carried out in 35 cycles, each amplification cycle comprising 95°C × 1 min (denaturation), 40°C × 1 min (annealing), and 72°C × 1 min (synthesis). The amount of each receptor kinase group expressed

was quantified by analyzing an image obtained by staining the PCR reaction product with ethidium bromide after agarose gel electrophoresis (4%) (Figure 1). For the purpose of standardization, each amount of expression was obtained as the ratio to the amount of β -actin expressed in the same sample. The numerical figures in Figure 1 indicate the amounts of expression at the various time points with the amount of expression in the absence of cyproterone acetate taken as 1.--

Please substitute the following paragraph [71] for paragraph [71] on pages 21-22 of the specification.

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[71] β -actin was amplified in 25 cycles of amplification (95°C \times 0.5 min, 60°C \times 1 min, 72°C \times 0.5 min) using 5'-ATCTGGCACCACACCTTCTACAATGAGCTGCG (sense) (SEQ ID NO:12) and 5'-CGTCATACTCCTGCTTGCTGATCCACATCTGC (antisense) (SEQ ID NO:13) as primers.--

MARK-UP OF THE CLAIMS SHOWING CHANGES MADE

4. (AMENDED) The composition as claimed in claim 3, wherein said LH-RH derivative is a peptide represented by the formula:

5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO: 1)

wherein Y represents a residue selected from among DLeu, DAla, DTrp, DSer(tBu), D2Nal and DHis(ImBzl); Z represents NH-C₂H₅ or Gly-NH₂, or a salt thereof.

5. (AMENDED) The composition as claimed in claim 3, wherein said LH-RH derivative is 5-oxo-Pro-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NH-C₂H₅ (SEQ ID NO: 2) or an acetate thereof.